REMARKS

Claims 4-15, 18-23, 39, 40, 42- 47, and 49-56 are pending in the application; of which claims 4, 5, 8, 9, 12, 18, 23, 40, and 42 are being amended, and claim 41 is being cancelled.

Claims 4, 5, and 13 are being amended to cosmetically improve the claim to recite "particulate microstructures" which is inherently implied by the terminology in the parent claim 39. Claims 12 and 23 are being amended with cosmetic changes to improve grammar. Claim 18 is being amended to correct the spelling of dioleoylphosphatidylcholine. Claim 40 is being amended to correct claim dependency since claim 41 is now cancelled.

The Examiner rejected claims 8-9 under 35 U.S.C. 112, second paragraph, on grounds that "wherein the powder composition has a fine particle fraction of greater than" is vague and indefinite. Claims 8 and 9 have been amended to recite that the inhaleable powder composition comprises particulate microstructures in a fine particle fraction of greater than 20% w/w. This amendment clarifies that the fine particle fraction refers to the particulate microstructures.

The proposed amendments to claims 4-5, 8-9, and 12 only make express, recitation of a feature that was already inherent in the original claim, and thus, is not a narrowing of the scope of the properly construed claim. <u>TurboCare v. General Electric Co.</u>, 264 F.3d 1111 (Fed. Cir. 2001); <u>Bose Corp. v. JBL, Inc.</u>, 274 F.3d 1354 (Fed. Cir. 2001); and <u>Interactive Pictures Corp. v. Infinite Pictures, Inc.</u>, 274 F.3d 1371 (Fed. Cir. 2001). Consequently, the scope of the doctrine of equivalents applied to the claim should not be limited under the rules of Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, (May 28, 2002).

Amendments to the Specification

This amendment is deleting paragraphs and language from some portions of the original Specification and adding language to other portions of the Specification. It is believed the deleted and added paragraphs add no new matter, and thus, should be entered. For example, the language added to the DESCRIPTION OF THE INVENTION section of the Specification is a restatement of language being deleted from the SUMMARY OF THE INVENTION section.

The Specification is also being amended at the paragraph beginning on line 20 on page 14, to add two more exemplary phospholipids useful in the disclosed stabilized preparations; dilauroylphosphatidylcholine, dioleoylphosphatidylcholine. Support for these two phospholipids can be found in parent PCT Application No. US98/20602, filed September 29, 1998, in claims 8, 22 and 50.

Rejection under 35 U.S.C. § 102(e) of Claims 40, 47 and 56

The Examiner rejected claims 40, 47 and 56 under 35 U.S.C. § 102(e) as anticipated by Unger (6,120,751).

Claims 40 is being amended to include the limitations of claim 41 which is now being cancelled. Claim 40 is to an inhaleable powder composition comprising a plurality of particulate microstructures, said microstructures comprising a structural matrix comprising calcium, an active agent and a phospholipid, wherein said phospholipid comprises a gel to liquid crystal transition temperature of greater than 40°C, and wherein said microstructures have a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

Claim 41 was not rejected under section 102(e), and accordingly, Unger does not teach claim 40 which now incorporates claim 41.

Rejection under 35 U.S.C. § 102(a) of Claims 40, 47 and 56

The Examiner rejected claims 40, 47 and 56 under 35 U.S.C. § 102(a) as anticipated by Eistetter (WO 97/26863).

Claims 40 is being amended to include the limitations of claim 41 which is now being cancelled. Claim 40 is to an inhaleable powder composition comprising a plurality of particulate microstructures, said microstructures comprising a structural matrix comprising calcium, an active agent and a phospholipid, wherein said phospholipid comprises a gel to liquid crystal transition temperature of greater than 40°C, and wherein said microstructures have a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

Claim 41 was not rejected under section 102(a), and accordingly, Eistetter does not teach claim 40 which now incorporates claim 41.

Rejection Under 35 U.S.C. § 103(a) of Claims 4, 8-15, 18-23, 39-47, 49-50 and 55-56

The Examiner rejected claims 4-15, 18-23, 39-47, 49-50 and 55-56 under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. (US 5,855,913) in view of Unger (6,120,751).

The Examiner states that Hanes et al. teaches aerodynamically light particles for drug delivery to the pulmonary system that have a tap density of less than 0.4 gm/cm^3, an aerodynamic diameter of 3 microns, and mass mean diameter between 5 and 30 microns. The Examiner further states that Table 2 of Hanes et al. teaches porous microparticles with DPPC have a density of 0.30 g/cm^3.

The Examiner admits that Hanes et al. does not teach the use of calcium in the structural matrix. However, the Examiner further states that Unger teaches that prior art studies have described the effects of calcium and other multivalent ions on membrane

asymmetry, lipid distribution, vesicle size, aggregation, and fusion.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a), there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the different references. Second, there must also be a reasonable expectation of success for such a combination. Also, the prior art references that are combined must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). "In making the assessment of differences between the prior art and the claimed subject matter, section 103 specifically requires consideration of the claimed invention 'as a whole.'" Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. (Fed. Cir., No. 04-1493, 6/9/05). "[S]imply identifying all of the elements in a claim in the prior art does not render a claim obvious. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). Instead section 103 requires some suggestion or motivation in the prior art to make the new combination. In re Rouffet, 149 F.3d 1350, 1355-56 (Fed. Cir. 1998). In determining the differences between the prior art and the claims, the question under 35 U.S.C. §103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Stratoflex, Inc. v. Aeroquip Corp., 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983). The benefits of the claimed invention should be viewed without the benefit of impermissible hindsight vision afforded by the claims themselves.

Claim 39 et al.

Independent claim 39 is to an inhaleable powder composition comprising a plurality of particulate microstructures. The particulate microstructures have a structural matrix comprising an active agent, calcium, and a phospholipid, and a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

As acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in the structural matrix. Furthermore, Unger does not provide any motivation which would suggest application of calcium to the Hanes et al. teachings. The section of

Unger quoted by the Examiner teaches:

> Studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. Although the underlying physical causes for the phenomena are debatable, general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to aggregate into larger, multilamellar structures and promotes fusion. Barium and strontium ions have also been investigated in this regard. Duzgunes et al., Biochemistry, 23:3486-3494 (1984). Species of phospholipids that are particularly pronounced in these effects are the subjet of investigation, as described, for example, by Leckband, et al., Biochemistry 32:1127-1140 (1993), Tilley et al., Biogenic Amines, 5:69-74 (1988) and Kwon, et al., Colloids and Surfaces B, 3:25-30 (1994).
>
> Other areas of investigation focused on the effect of calcium-induced aggregation on phase transition temperature and whether aggregation and fusion phenomena have a temperature dependance. Duzgunes, supra, Kwon, supra, and Tilcock et al., Biochemistry, 23:2696-2703 (1984). The effects of calcium-induced aggregation are so pronounced that efforts have been undertaken to limit the effect in order to control the size of liposomes used in drug delivery systems by forming vesicles in which calcium ions are confined to outer surfaces of the bilayer. European Patent Publication EP 579 703....

[Emphasis added]. (Unger Col. 1, line 50 to col. 2 line 9.)

Thus, Unger teaches that calcium causes aggregation of phospholipid vesicles. Such an aggregation teaches away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures which are separate and discrete particles and substantially not aggregated in the powder

composition. As taught in the present application, aggregation of particles is undesirable to maximize the dispersibility of the powder composition:

> In order to maximize dispersibility, dispersion stability and optimize distribution upon administration, the mean geometric particle size of the perforated microstructures is preferably about 0.5-50 μm, more preferably 1-30 μm. It will be appreciated that large particles (i.e. greater than 50 μm) may not be preferred in applications where a valve or small orifice is employed, <u>since large particles tend to aggregate or separate from a suspension which could potentially clog the device</u>.

(Specification, page 32, lines 11-16.)

> With respect to the advantageous deposition profile provided by the instant invention it is well known that MDI propellants typically force suspended particles out of the device at a high velocity towards the back of the throat. Since prior art formulations typically contain a significant percentage of large particles and/or aggregates, as much as two-thirds or more of the emitted dose may impact the throat.

(Specification, page 39, lines 24-28.) Thus, the Specification teaches that aggregated particles are undesirable because they tend to separate from a suspension and clog the inhaler device. Also as explained, prior art formulations typically contain a significant percentage of large particles and/or aggregates which result in a large percentage, as much as two-thirds or more of the emitted dose, impacting the throat and not deep into the lungs, which is desired in inhalation therapy.

Thus, the combination of Unger and Hanes at al. does not provide the suggestion or motivation, to selectively extract calcium from Unger and combine it with the teachings of Hanes et al., to derive claim 39. Hanes et al. makes no mention of calcium. Unger teaches away from calcium addition because Unger teaches that calcium addition results in aggregation of the claimed particulate microstructures, which as explained above is undesirable for inhalation. If the particulate microstructures were extensively aggregated, a large percentage of the particulate microstructures of the inhaleable powder composition would undesirable impact the throat limiting delivery of the drug to the lungs where it is needed. Thus, the Examiner has simply identified particular elements of the claim in the prior art without providing some suggestion or motivation in the prior art to

make the new combination. The combination suggested could only have been derived in hindsight based on the actual combination taught by Applicant's claim itself.

Furthermore, Hanes et al. teaches that an organic solvent dissolved polymer is suspended in an aqueous medium containing a surface active agent, such as PVA, to form an emulsion that is stirred until the organic solvent evaporates to leave behind particles. If such a composition were aggregated with the addition of calcium, the resultant composition would have large aggregated particles which may very well not have the particle sizes described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences that Hanes et al. teaches against the use of a calcium aggregating agent as taught by Unger.

Further, claim 39 is to a powder composition comprising particulate microstructures having a mean aerodynamic diameter <u>of less than 5 microns</u>. In contrast, Hanes et al. teaches that it is desirable to have particles with "a diameter within a selected range <u>of at least 5 μm</u>." Repeatedly, in column 7, lines 54 to column 8, line 67, Hanes emphasizes that the desirability of particles sized at least 5 μm and in the range between about 5 and 30 μm. Thus, Hanes teaches away from the claimed particle size limitation, and does not teach the desirability of particles having a mean aerodynamic diameter of less than 5 microns as claimed in claim 39. Unger does not make up for the deficiencies of Hanes, because Unger also does not teach particulate microstructures having a mean aerodynamic diameter of less than 5 microns as claimed.

Furthermore, neither Hanes et al. nor Unger teach particulate microstructures having a bulk density of less than about 0.5 g/cm^3. Hanes et al. teaches particles having a tap density of less than 0.4 gm/cm^3. The tap density of a powder is obtained by repeatedly tapping a vessel containing the powder until the volume of the powder in the vessel does not decrease any further. Thus, tap density is affected by the size and shape of the vessel, the amplitude of the taps, and the frequency of the tapping, amongst other factors. The bulk density of a powder is the weight of the powder per unit of volume compared to the weight of the same volume of water, measured for example, in a graduated cylinder. Thus, the tap density value is affected by the flow and rheological

properties of a powder, while the bulk density measurements are not subjected to these factors. Thus, a tap density measurement is not the same as a bulk density measurement.

Thus, when claim 39 is considered as a whole, Hanes et al and Unger do not teach an inhaleable powder composition comprising particulate microstructures with calcium and phospholipid, the particulate microstructures having a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3. One of ordinary skill in the art would not have found it obvious to modify Hanes et al. based on the teachings of Unger, and more specifically, one of ordinary skill in the art would have no reason to selectively extract the calcium taught by Unger et al. and insert this calcium into the polymers taught by Hanes et al., and also would not be taught to make particles having the claimed mean aerodynamic diameter of less than 5 microns.

Claims 4-15, 18-23, 52, 53 and 55 depend upon claim 39, and are patentable over the cited references for the same reasons as claim 39, from which they depend. In addition, these claims recite additional distinguishing features. For example, claim 4 recites that the microstructures are porous which is not taught by the cited references. Claim 12 recites that the microstructures are hollow and porous. Claim 15 recites that the mean geometric diameter is less than about 5 microns. Thus at least claims 4, 12 and 15 are further patentable over the cited references.

For these reasons, claim 39 and its dependent claims are not rendered unpatentable by Hanes et al. in view of Unger. Accordingly, the Examiner is respectfully requested to allow claim 39 and against dependent therefrom.

Claim 40 et al.

Independent claim 40 is also not rendered unpatentable by Hanes et al. in view of Unger.

Claim 40 is to an inhalable powder composition comprising a plurality of particulate microstructures that include a structural matrix comprising calcium, an active agent, and a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, and wherein said microstructures have a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

The Examiner has also failed to establish a *prima facie* case of obviousness against claim 40, because there is no suggestion or motivation in the references themselves to combine their teachings. As acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in the structural matrix. Unger teaches that a general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to aggregate into larger, multilamellar structures and promotes fusion. Unger further teaches that species of phospholipids are particularly pronounced in these effects. Such an aggregation teaches away from the claimed inhaleable powder composition comprising a plurality of un-aggregated particulate microstructures and the rejection does not provide a reasonable expectation of success to achieve the claimed invention. Furthermore, the aggregation of phospholipid vesicles with calcium, as taught by Unger, would reduce the dispersibility and dispersion stability of the claimed particulate microstructures, as the aggregated particles could potentially clog an inhaler device. Further, large aggregated particles have a greater tendency to impact the throat, and as a consequence, provide less particle deposition into the lungs as desired. Thus, Unger and Hanes at al. provide no suggestion or motivation, to selectively extract calcium from Unger and combine it with the teachings of Hanes et al. to derive claim 40.

Furthermore, if the Hanes et al. composition were aggregated with the addition of calcium, the resultant large aggregated particles may well not have the particle sizes described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences that Hanes et al. teaches against the use of a calcium aggregating agent. Also, claim 40 is to a powder composition comprising particulate microstructures having a mean aerodynamic diameter of less than 5 microns. In contrast, repeatedly, in column 7, lines 54 to column 8, line 67, Hanes emphasizes the desirability of particles sized at least 5 µm. Thus, Hanes teaches away from the claimed mean aerodynamic diameter of less than 5 microns as claimed in claim 40. Furthermore, neither Hanes et al. nor Unger teach particulate microstructures having a bulk density of less than about 0.5 g/cm^3 and instead only teach tap density.

Furthermore, that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, is also not taught are suggested by the cited references. Nor is this teaching to a particular minimum temperature obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

Thus, when claim 40 is considered as a whole, the combination of Hanes et al. and Unger clearly do not teach or suggest the claim, without the benefit of impermissible hindsight vision afforded by the claim itself. The cited references do not teach or suggest a powder composition comprising particulate microstructures that not only include a structural matrix comprising calcium, an active agent, and a phospholipid, but that also recite that the phospholipid should have a gel to liquid crystal transition temperature of greater than 40°C. For these reasons, claim 40 and the claims dependent therefrom, are not rendered unpatentable by Hanes et al. in view of Unger.

Rejection Under 35 U.S.C. § 103(a) of Claims 51-52

The Examiner rejected claims 51-52 as being unpatentable over Hanes et al. in view of Unger and further view of Igarashi (4,201,774). This rejection is respectfully traversed.

Claims 51 and 52 are to an inhalable powder composition in which bioactive agent is an aminoglycoside antibiotic. Claims 51 is dependent upon claim 40 and claim 52 is dependent upon claim 39.

As acknowledged by the Examiner, Hanes et al. does not teach the use of aminoglycoside antibiotic or calcium. Unger teaches that multivalent cations, such as calcium and magnesium, cause phospholipid vesicles structures to aggregate into larger, multilamellar structures and promote fusion. Unger further teaches that species of phospholipids provide particularly pronounced aggregation effects. Thus, Unger teaches that calcium addition causes aggregation of phospholipid vesicles, and consequently teaches away from the claimed inhaleable powder composition comprising a plurality of particulate microstructures. The aggregation of phospholipid vesicles with calcium, as taught by Unger, would reduce dispersibility and dispersion stability of the particulate microstructures of the claimed composition. The aggregated particles would potentially clog an inhaler device and have a greater tendency to impact the throat to provide less particle deposition into the lungs. Igarashi also does not teach particulate microstructures comprising phospholipid, calcium and an active agent. Thus, the cited references do not provide any motivation to derive the claimed powder composition comprising particulate microstructures comprising phospholipid, calcium and an active agent as recited in claims 39 and 40.

Also, claims 39 and 40 both recite a powder composition comprising particulate microstructures having a mean aerodynamic diameter of less than 5 microns. In contrast, Hanes emphasizes the desirability of particles sized at least 5 μm. Thus, Hanes teaches away from the claimed mean aerodynamic diameter of less than 5 microns. Also, neither Unger nor Igarashi teach the desirability of particles having a mean aerodynamic diameter of less then 5 microns. Furthermore, Hanes et al., Unger and Igarashi do not teach particulate microstructures having a bulk density of less than about 0.5 g/cm^3 as claimed in claims 39 and 40.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of

greater than 40°C, as claimed in claim 40. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, the Examiner respectfully requested to allow claims 51 and 52 over the cited references.

Rejection Under 35 U.S.C. § 103(a) of Claims 53-54

The Examiner rejected claims 53-54 as being unpatentable over Hanes et al (US 5855913) in view of Cohen et al (5149543) in further view of Benson et al (5,006,343). This rejection is also respectfully traversed.

Claims 53 and 54 are to an inhaleable powder composition that includes a bioactive agent that is a fungicide. Claims 53 depends upon claim 39 and claim 54 depends upon claim 40.

Claims 53 and 54 are patentable for the same reasons as claims 39 and 40, respectively, from which they depend.

As acknowledged by the Examiner, Hanes et al. does not teach the use of fungicides or calcium. Unger teaches that multivalent cations, such as calcium and magnesium, cause phospholipid vesicles structures to aggregate into larger, multilamellar structures, and further teaches that species of phospholipids are particularly pronounced in these effects. Unger teaches away from the claimed inhaleable powder composition comprising a plurality of particulate microstructures comprising phospholipid and calcium, because the aggregation of phospholipid vesicles with calcium would reduce dispersion stability of particulate microstructures as claimed. The aggregated particles would also potentially clog an inhaler device and have a greater tendency to undesirably impact the throat and provide less particle deposition into the lungs. Benson also does not teach a particulate microstructure comprising phospholipid, calcium and an active agent. Thus the cited references do not provide any motivation to derive the claimed powder composition

comprising particulate microstructures comprising phospholipid, calcium and an active agent as recited in claims 39 and 40.

Also, claims 39 and 40 both recite a powder composition comprising particulate microstructures having a mean aerodynamic diameter of less than 5 microns. In contrast, Hanes et al. emphasizes the desirability of particles sized at least 5 µm. Thus, Hanes et al. teaches away from the claimed mean aerodynamic diameter of less than 5 microns. Also, neither Unger nor Igarashi teach the desirability of particles having a mean aerodynamic diameter of less than 5 microns. Furthermore, Hanes et al., Unger and Igarashi do not teach particulate microstructures having a bulk density of less than about 0.5 g/cm^3 as claimed in claims 39 and 40.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 40. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, the Examiner respectfully requested to allow claims 53 and 54 over the cited references.

Provisional Double Patenting Rejections

The provisional double patenting rejections will be addressed upon indication of allowable subject matter in the present application, since the double patenting rejection is provisional.

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES, P.C.

Date: March 27th, 2006

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